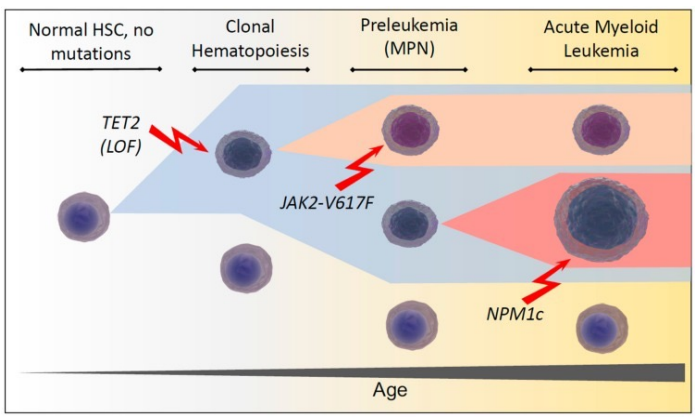
A CHIP off the old block - Clonal Hematopoiesis of Indeterminate Potential and Age Related Diseases

Aging is the time dependent decline of physiological functions vital for survival that can eventually lead to diseases, such as cancer, neurodegenerative diseases, and cardiovascular disorders. It is defined by several hallmarks (1), which are associated with an increase in somatic mutation across several tissues (2). Manifesting as different classes of mutations, for example the spontaneous deamination of 5-methlycytosine to thymine, and small insertions and deletions. The majority of these mutations are phenotypically silent. However, through the phenomenon of Darwinian selection, some mutations can potentially induce a competitive advantage to the cell, prompting clonal expansion (3). Clonal hematopoiesis refers to the clonal expansion within hematopoietic stem cells (HSCs) from a single mutated stem cell which can potentially lead to the development of blood cancers such as leukemia, lymphoma, and myeloma. These mutations can also occur from exposure to environmental factors such as radiation or chemicals and is becoming increasingly recognized as a significant risk factor for the development of blood cancers (4), therefore research is vital to better under its implications for patient care. Clonal hematopoiesis of Indeterminate potential (CHIP) is often asymptomatic and is usually detected incidentally during routine blood tests. Treatment for CHIP is not yet well-established, and many patients with the condition may not require any intervention (5).

The exact mechanisms by which CHIP leads to blood cancer are not yet fully understood. One theory is that the accumulation of mutations in HSCs can lead to the production of abnormal blood cells, which can eventually develop into cancerous cells. Another possibility is that the mutations create a permissive environment for the growth of cancerous cells in the bone marrow (6). However recent studies have highlighted several genes to be implicated in CHIP, with some of the most commonly mutated genes include DNMT3A, TET2, ASXL1 (7) and JAK2 (8).



Although CHIP is thought to occur in up to 10% of individuals over the age of 70 and is associated with an increased risk of hematologic malignancies, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (7) (figure 1), recent research has suggested CHIP may have broader implications for age-related diseases beyond the hematologic system.

Figure 1. Schematic representation of clonal hematopoiesis and aging and the development of acute myeloid leukemia from mutations in genes such as Janus Kinase 2 (JAK2-V617F) (8)

One of the most intriguing aspects of CHIP is its association with non-hematologic diseases, particularly cardiovascular disease (CVD) (Figure 2). Studies have shown that individuals with CHIP are at a higher risk of developing CVD, independent of traditional risk factors such as age, sex, smoking status, and cholesterol levels (9). This association is thought to be driven by the clonal expansion of HSCs with mutations that affect genes involved in the regulation of inflammation and immune responses, which can contribute to the development of atherosclerosis and other vascular disorders.

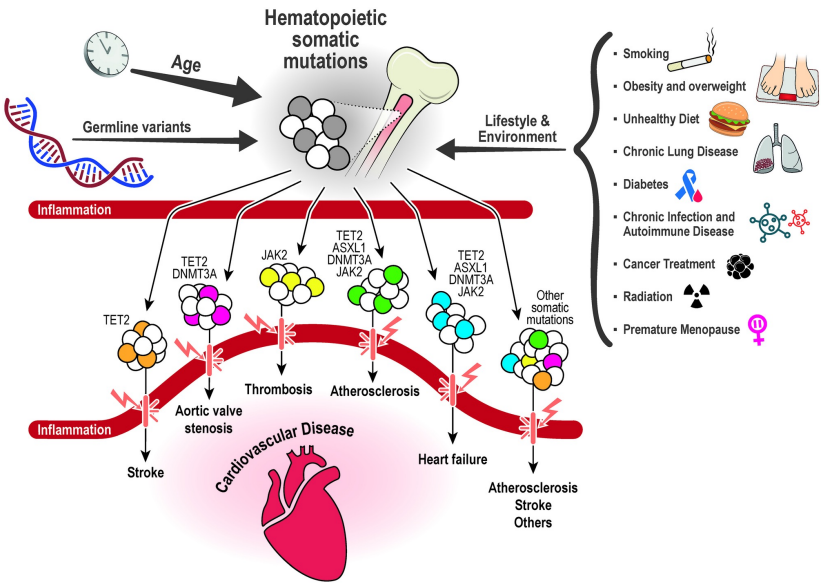


Figure 2. Schematic representation showing the induction of somatic mutations leading to cardiovascular disease (16).

In addition to CVD, CHIP has also been linked to other age-related diseases, including solid tumors (10), neurodegenerative disorders, such as Alzheimer's disease (11), and chronic kidney disease (12). These associations suggest that the effects of CHIP may extend beyond the hematologic system and involve broader changes in cellular function and metabolism.

The relationship between CHIP and age-related diseases raises important questions about the underlying biology of aging and the mechanisms that drive the development of disease in later life. It also highlights the potential for early detection and intervention to prevent or delay the onset of age-related diseases. For example, recent studies have suggested that the presence of CHIP may be a useful biomarker for predicting the risk of developing various diseases, which could allow for targeted screening and prevention strategies (13).

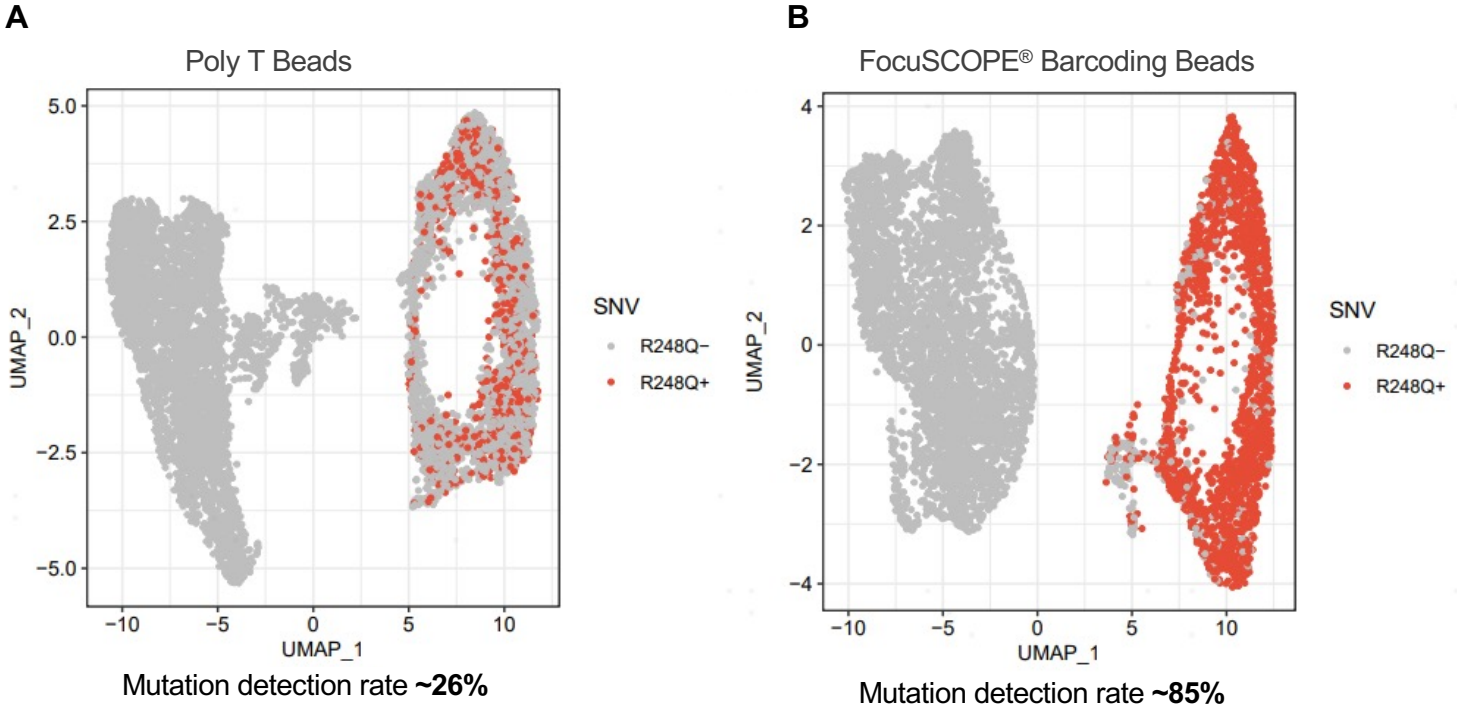
Recently, researchers have adopted high throughput sequencing to study CHIP. A study by Jaiswal et al examined the presence of CHIP in healthy individuals. They analyzed blood samples from over 17182 individuals and found that clonal hematopoiesis was present in over 10% of individuals over the age of 70 (7). A recent study used single-cell sequencing to identify the mechanistic link between DNMT3A (R882) mutations and aberrant transcriptional phenotypes in clonal hematopoiesis (15).

To facilitate research into CHIP, Singleron has developed the novel FocuSCOPE® Single Cell Multiomics mRNA x Clonal Hematopoiesis Kit**. This kit enables researchers to simultaneously analyze gene expression and common clonal hematopoiesis mutations at the single-cell level,** which can provide valuable insights into the underlying molecular mechanisms of CHIP-related diseases and aging process. Uniquely designed barcoding beads with target specific capture probes enable high-throughput and high-accuracy profiling of CHIP mutations in single cells.

Common CHIP mutations covered by the kit:

Gene	Target site
DNMT3A	R882H
TET2	I1873T/*/N , R1261H/C , R1359C/H/S/G , H1380Y/P/Qfs*68/R
TP53	R175H,G245S, R248Q, R248W, R249S,R273H, R273S, and R282W
ASXL1	p.G643WfsX12
JAK2	V617F

High detection rate compared to poly-T capturing only



Mutation detection rate **~26%**

Mutation detection rate **~85%**

Figure 3. CCRF and K562 were mixed in equal proportions. Libraries were prepared in the same way by either specially designed FocuSCOPE barcoding beads (B) or Poly T beads (A). CCRF cell line contains TP53 mutation (R248Q), whereas K562 doesn't contain this mutation. Target enrichment by FocuSCOPE beads dramatically increases the detection sensitivity of the mutation.

All-in-One service available in Europe

Our all-in-one single cell sequencing service can help you to get a quick start with single cell multi-omics CHIP study. Every project commences with a complimentary consultation specifically designed to cater to your unique requirements. Once the project is customized to your satisfaction, a dedicated project manager is assigned to accompany you throughout the entire process. Upon receiving the samples, the remaining workflow, including single cell sequencing library construction, sequencing, and data analysis, is seamlessly executed within our state-of-the-art service lab located in Cologne.

Ordering Information

Product	2 RXNs / 16 RXNs
FocuSCOPE® Single Cell Multiomics mRNA x Clonal Hematopoiesis Kit	4341011/4341012
FocuSCOPE® Single Cell Multiomics mRNA x Clonal Hematopoiesis Kit for Matrix	4341021/4341021

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